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E D I T O R I A L

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful—the editor, alone, is responsible for their type, their tone and their tenor.

"I WENT IN SEARCH OF FLOWERS"

I WENT in search of flowers the other day where the deer-trail leaves the White Horse Pike and winds its way to Weymouth. This is a countryside rich in floral treasures, with every month, from Spring to Fall, a time of new display. Cedar water, brown as the back of a wood-thrush, silently—solvently—spreads through tangled wilds, diffusing everywhere its living vigor, and sand that elsewhere might have stayed as sand is here a soil inspired. For sheer variety of bush and bloom I know no local soil so spendthrift. There are lush spots for the water-lovers and high and dry spots for greens less demanding. The soil's potential hydrogen cavorts over an obliging range, and for the humblest lichen to the tallest pine, the bogs distill a perfect benediction.

Small fruit plants, the cran, the rasp, the black and the huckle grow here with gay abandon, yet in season wondrously heavy with berry.

The hardy evergreens and ericaceous plants divide the humus heath beneath them but leaving room, and room enough for a vast array of others of God's green children.

Here, in certain secluded spots, when April rains away the remnant snows, one may gladly go arbutusing and elsewhere in September see the swaying cardinal flower, like a crimson flamingo, knee deep in water, peeping through smilax curtains at its landlubber, but not less lovely, blue brother lobelia.

And here, in season, and in the proper places are orchids exotic, —the pogonias, arethusas, cypripediums, ladies' tresses, and here too are the sundews, the liatris, the rues, the mints, and oddly enough a queer cactus or two.

But queerest of all, on Weymouth road, is the cannibal sarracenia, carnivorous scoundrel of the bogs, who daily feeds on murdered insects.

Few folks know that even in the floral family there are members whose codes of living are crafty and cruel, and not at all in harmony with the codes of their kindly kindred.

And the sarracenia (pitcher-plant of the Weymouth bogs) is not the only local vampire. There are Droseras (the sundews of Lake's pond) and, believe it or not, the hypocrite Jack-in-the-Pulpit, who dominates, in early Spring, the moist wide wastes of Weymouth. And who but a lens-toting, net-chasing, goggled academician would ever suspect the happy-go-lucky Jack-in-the-Pulpit of being a pirate of old, cruel and bold, living and thriving on blood and gold. *Arisæma triphyllum* to the high brow, Jack-in-the-Pulpit or Indian turnip to the boy of the country side,—and a fine sort of a preacher is Jack,—standing in Episcopalian rectitude and Presbyterian complacency in a pulpit of many colors, with his sounding board high over his head, and his eye ever staring far into the light of heaven. Jack belongs to a respectable enough family, for even the chaste Lily of Calla, upstanding and proud, only inherits her lovely white form from the same forbears as Jack.

But the pulpit of Jack is only a snare and a delusion. His clerical mien hides an ingrate's ambitions, and many the poor wandering soul coming to Jack for beauty finds only lingering death down at the foot of his pulpit. Jack the Pharisee, unlike his blatant brother, the sarracenia, is not a true insect-eating monster, but like the sarracenia he is given to soggy surroundings, and his pulpit is never better built than when it rises in dignity out where the air is humid and the woodlands damp and shady. And so beneath his bowered cathedral arches he holds forth in gay abandon.

To his shrine come congregations of curious gnats and other winged worshippers. The bullfrog and mottled green toad strum their basso notes until the old cathedral hums with holy music, and to the tune of vibrant notes the gnats march on to reverent worship that only ends with heartless sacrifice. On to the slippery pulpit of Jack the winged folks alight, and they no sooner perch on the fatal forum than their little feet slide down the inside walls of the well-greased colored column. Descent into the trap is very easy indeed, but pity the poor creature who tries to climb back. For that is generally such a hopeless task. So the little deluded worshipper finding a return impossible, goes on and on, and down near the base of the pulpit he comes upon a sacramental ledge where staminate florets

exude their fertile pollen. Blundering through these pollen-laden crypts the penitent is swathed in dusty embrace, and on he wanders past into the chamber where the tiny pistillate florets await him to perform his vitalizing penance unaware.

But despite this gracious life-perpetuating act, Jack is still a sycophant, a rank, a gay deceiver, for often our little unsuspecting fly is held a hopeless prisoner. There is no way of escape. Efforts to crawl up the slippery surface are without avail and eventually weak from their constant climbing, the victims, hungry and exhausted, fall prey to the wiles and whims of this arrant murderer of innocent well-doers. Merciful nature sometimes sends her gracious rain to drown the little victims and so reduce their time of pain and stress.

May is Jack's big month at Weymouth, and those who doubt will get confirmation of our story of his treachery by opening a few of Jack's pulpits and noting at the base of his malevolent shrine—poor little victims sacrificed heartlessly to the imperfection of Jack's regenerative system. Or even now, in Weymouth, the pitcher-plant confirms us.

And so do we often find in nature this peculiar sacrifice of the higher life to the lower. The cuckoo-pint plants its toxic seed in the body of a living bird, so that the seedlings may find a powerful fertilizer in the decaying flesh into which to strike their rootlets—and the sarracenia burns up the death sweat of insects to keep its fires aglowing.

The Master of philosophers, who asked his listeners to consider the lily of the field, clinched well his fertile simile, for in the intricacies of a single blossom are lessons enough for all who search and see aright. In the essence of the rose, in the sleep of the evening primrose, and in the cannibal tricks of the pitcher-plant, are divergent enough characters, to warrant in truth the oft-quoted assertion that man with all his learning, can study, with profit, the sermons in stones and the books in humble blossoms.

And Weymouth woods, and Weymouth bogs are rich and ready with lore and lure for all who seek and find their joys in Nature's elemental grandeur!

IVOR GRIFFITH.

ORIGINAL ARTICLES

RHUS GLABRA

G. H. McFadden* and R. L. McMurray**

Long recognized in the several schools of medicine as possessing valuable medicinal properties, Rhus Glabra, is now out of the Pharmacopoeia. It has still a place in medicine however and the Authors have in this article added much authoritative data to its strangely meager literature.

THE recorded history of *Rhus glabra* Linné does not date back as far as many of our common medicinal plants, although it was undoubtedly used by the North American natives for a long time before it was known to the white man. When the Europeans first came to America, they found the Indian using the berry of the sumac for its red coloring principle and as a medicine.

In 1621, Bauhin [1] described *Sumach angustifolium* as a plant having a compound leaf with eleven or twelve crenately margined leaflets. Later, he named the plant *Rhus angustifolium.* Linné [2] believed this plant to be the same as the plant to which he gave the name *Rhus glabra* in his binomial system of nomenclature, which was published in 1753.

Greene,[3] in 1906, pointed out that the plant is widely distributed. In this distribution over a range of climatic conditions, a number of variations occur. Greene made a segregation of these varieties, selecting as the true *Rhus glabra,* that variety common throughout Pennsylvania, southern Maryland and Virginia. He found that nearly all the *Rhus glabra* plants from other regions vary in one or more details from the Pennsylvania variety. His critical reclassification resulted in twenty-nine different species, twenty-four of which were new.

The official synonym for the fruit of *Rhus glabra* Linné is Sumac Berries. This term is widely used as a trade name for the crude drug.

Many synonyms have been used to characterize the plant, *Rhus glabra* Linné. The most common of these is *smooth sumac.*[4] The

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plant is popularly known as *Pennsylvania sumac,*[5] *upland sumac,*[5] *Carolina sumac,*[4] *common sumac,*[4] *scarlet sumac,*[4,5] *sleek sumac,*[4,5] *senhalence,*[4,5] *shoe-make,*[4,5] *white sumac,*[4,5] *vinegar tree,*[4,5] *mountain sumac,*[5] *New England sumach,*[6] *Buck's horn tree,*[4] and *der virginischer Sumach.*[4]

Rhus glabra is indigenous to the central and eastern states of the United States and to southern Canada. It is found, often with variations, in every state of the United States. In mountainous areas the shrub is more or less confined to the warmer valleys. It is abundant on barren hillsides, in thickets, and on waste ground throughout Ohio.

Rhus glabra is an entirely glabrous shrub, from three to fifteen feet high. The branches are irregular and straggling. The plant has a large amount of resinous, milky sap.

The leaves are alternate, imparipinnate and deciduous, with eleven to thirty-one leaflets. The leaflet is ovate-lanceolate, with a serrate margin; dark green above and whittish beneath.

The inflorescence is an erect, thyrsoid panicle. The flowers are more or less polygamous, often dioicious. The calyx is small, five-parted and covered with short hairs. The corolla is five-petaled. The petals are greenish-yellow or crimson. In the sterile flower there are five stamens. In the fertile flower the ovary is globular, sessile, one-celled and clothed with a silky villus. The stigma is subsessile.

The fruit is a flattened ovoid, nearly globular or somewhat reniform drupe; externally dark red, velvety with short hairs. The hairs are clavate and consist generally of three cells. The seed is brown and very hard.

The root system is of the creeping type and is located near the surface of the ground. The creeping root frequently throws out adventitious shoots, enabling the plant to propagate very rapidly.

A cross-section study of the root shows a large, well-defined pith. Immediately adjacent to the pith is the xylem, its cells in radial rows. The cambium is a thin zone of small, thin-walled cells of rectangular section, having the appearance of tiers of bricks. The phloem consists of irregularly arranged cells above the cambium. Resin canals associated with each vascular bundle are situated in the phloem. Adjacent to the canal is the pericycle consisting of a patch of heavy-walled cells. The phloem is ringed about with a cortex which is protected by an epidermis. Lining the resin canal is an epithelial layer which appears to be composed of secreting cells. There is a radial alinement

around the canal to a depth of five cell diameters, indicating secondary activity in this part of the phloem, and an encroachment of cells on the cavity of the canal.

The leaves and bark of *Rhus glabra* are extensively used in the tanning of leather. The wood has been used in cabinetmaking. The fruit and bark of the root are used in medicine. The infusion made from the fruit is used as a cooling drink and refrigerant in fevers. The fluidextract is highly astringent and has been considerably used as an astringent gargle and mouth wash for ulcerations and stomatitis.

Rhus glabra was defined in the U. S. P. X as the dried ripe fruit of *Rhus glabra* Linné (Fam. Anacardiaceæ). It has been official in every edition of the U. S. P. except the ninth and eleventh revisions. The drug was included in the secondary list of Materia Medica in the first U. S. P. published in 1821. In the sixth revision a short description of the crude drug was given for the first time. In 1916 the drug was discontinued from the U. S. P., but was included in the N. F. IV. The Homeopaths also include *Rhus glabra* in their pharmacopœia, but specify the bark of the root as the official part used for making a tincture.

An extensive search reveals that the literature on the chemistry of this plant is rather limited and somewhat conflicting in content. The earliest work of a chemical nature so far uncovered was that of Cozzens,[7] who concluded that "the acid of the sumach is malic, and that it is nearly pure, being only contaminated with a small portion of gallic acid." However, Rogers [8] proved that the malic acid existed in sumac as calcium acid malate. Almost seventy years later Frankforter and Martin [9] carried out the first analysis of the fruit, and found two different fixed oils from different parts of the fruit. Constants were determined on the oils and the percentage of moisture, ash, tannin, calcium acid malate and nonsaponifiable matter reported. Brubaker [10] made an ether extraction of the fruit and reported constants of the oil obtained by this method of extraction. In 1925 Peacock and Peacock [11] made an extended investigation of the tannin of *Rhus glabra,* and reported it to be gallotannic acid.

Experimental

The fruits were collected the first week of December, 1935. The place of collection was in the hilly region adjacent to U. S. Highway 40, in Licking County, Ohio, at a point 37 miles east of Columbus.

The entire panicles were removed from the plant and transported in sacks. After drying, the fruit was shelled out by hand, culled until the fruits were separated and the non-fruit portion discarded. The fruits were further air-dried at 30° C., after which they were cleaned by a motor-driven fanning mill. The milling removed 12.75 per cent. of refuse matter from the fruits. Approximately five pounds of the cleaned fruits were ground in a No. 6½ Quaker City mill. The material was further carefully reduced to a No. 20 powder with a No. 4 Quaker City hand mill.

Preliminary Investigation

(a) Moisture was determined by the toluene distillation [12] method and amounted to 5.25 per cent.

(b) A Dragendorff [13] selective solvent determination was made and calculated to both the air-dried and anhydrous condition (based on a moisture content of 5.25 per cent.) as follows:

	Air-dried Per cent.	Moisture-free Per cent.
Petroleum ether	12.42	13.10
Ethyl ether (absolute)	4.64	4.89
Ethyl alcohol (absolute)	11.82	12.47
Distilled water (aseptically controlled)	6.75	7.12
NaOH (0.2 per cent.)	3.74	3.94
HCl (1 per cent.)	3.01	3.17
Marc	48.54	51.22

(c) An ether extraction determination [12] gave the following results:

	Air-dried Per cent.	Moisture-free Per cent.
Total ether soluble extract	17.27	18.22
Volatile ether soluble extract	0.60	0.63
Non-volatile ether soluble extract	16.67	17.59
(d) Crude Fiber [12]	31.86	33.62
(e) Pentosan [14]	21.61	22.81
(f) Total Nitrogen [12]	1.32	1.39

	Air-dried Per cent.	Moisture-free Per cent.
(g) Arsenic [14]	None	None
(h) Ash determinations:		
Total ash [12]	2.55	2.69
Acid soluble ash [12]	2.27	2.39
Acid insoluble ash [12]	0.28	0.30
Water soluble ash [15]	0.95	1.00
Water insoluble ash [15]	1.60	1.69
Alkalinity of ash [15]	2.04	2.15

(i) The constants of the oil obtained from the petroleum ether extractive are as follows:

Refractive Index at 20° C.	1.4719
Density at 20° C.	0.9227
Optical Rotation at 20° C.	0.00
Acid Value [12]	8.97
Iodine Value [12]	87.17
Ester Value [12]	159.2
Saponification Value [12]	168.17

Constituents of the Ash

Sand and silica [14] were determined by the A. O. A. C. method. Iron,[14] manganese [14] and copper [14] were determined colorimetrically from aliquot portions of the filtrates obtained in the sand and silica determinations. From aliquots of this same solution, aluminum [14] and magnesium[14] were determined gravimetrically, calcium [14] volumetrically, and zinc [14] turbidiametrically. Sodium and potassium chlorides [14] were determined by the A. O. A. C. method. Sodium [16] was determined by the magnesium uranyl acetate method on a concentrated solution of the mixed sodium and potassium chlorides and reported as Na_2O. By calculation from the foregoing results, the potassium was determined by difference and reported as K_2O. Chlorides [14] were determined on a specially prepared sample. Sulfur [14] and phosphorus [14] were determined on a sample prepared by the sodium peroxide fusion method. The following table is a summary of the results:

	Per cent.		Per cent.
Sand	2.95	Copper	0.000
Silica	7.44	Zinc	0.078
Iron	0.86	Na_2O	4.16
Al_2O_3	4.67	K_2O	38.15
CaO	22.80	Cl	1.58
MgO	7.24	SO_3	7.15
Mn_3O_4	0.147	P_2O_5	21.17

Constituents of the Fixed Oil

One hundred and three pounds of the fruits were extracted with 95 per cent. alcohol in a Lloyd extractor. The alcoholic extractive was evaporated to a cream. The evaporation effected a separation of the fixed oil from the other extractive, which was mechanically removed. A total of 8.87 pounds of crude oil was obtained. The remaining alcohol soluble material amounted to 23.90 per cent. of the crude drug.

Fifteen hundred grams of the crude oil were subjected to steam distillation. The distillate thus obtained had a very distinct and characteristic odor resembling the odor of the freshly gathered fruit. The volatile oil obtained in this distillate was negligible in amount due to the airdrying of the crude drug and the evaporation of the alcoholic extract to a cream.

The fixed oil remaining after steam distillation was placed in solution with petroleum ether and the solution thoroughly washed with distilled water to remove any aqueous soluble fraction. The petroleum ether solution was evaporated on a steam bath until there was no further loss of weight. The purified oil obtained by this procedure amounted to 94.6 per cent. of the crude oil used. The pure oil was blackish-brown in color and had a green fluorescence. It had a characteristic odor and a bland taste. The acid value was 1.19; the saponification value was 176.70; and the iodine value was 94.15.

The aqueous fraction was extracted with petroleum ether to remove all traces of fixed oil. The aqueous fraction was then extracted with ether. The ether was allowed to evaporate spontaneously. A red-brown resin amounting to 1.87 grams was obtained. The aqueous fraction was filtered to remove plant parts and dirt. The solution was evaporated to dryness. A dark brown residue weighing 20.4 grams was obtained. This residue contained tannin and sugar.

Thirteen hundred and fifty grams of the pure fixed oil was saponified with an alcoholic solution of potassium hydroxide. The alcohol was recovered from the reaction mixture. The residue was a soft, dark-brown soap, having a peculiar characteristic odor.

The soap was extracted with ether to remove the unsaponifiable matter. The unsaponifiable matter amounted to 36.1 grams, corresponding to 2.67 per cent. of the oil used.

Ten grams of unsaponifiable matter were examined by the standard digitonin method.[17] The digitonide was washed with alcohol and ether to remove the hydrocarbon. The digitonide was then treated with boiling xylene for eight hours. The digitonin was recovered by filtration. The xylene solution was evaporated to dryness by means of a current of air. The residue gave the Liebermann-Burchard test [18] for sterols. The crude sterol was taken up with hot alcohol. On cooling, fine, white crystals were obtained. These were repeatedly recrystallized from hot alcohol. The melting point of the crystals was 137.2° C. The sterol acetate was prepared by refluxing the sterol with acetic anhydride. The sterol acetate was recrystallized several times from hot alcohol. The melting point of the sterol acetate was 117-118° C.

The alcoholic filtrate resulting from the digitonin treatment was evaporated to one-half of its original volume. A heavy red-brown precipitate settled out. This precipitate was repeatedly recrystallized from hot alcohol, ether, acetone, and glacial acetic acid until white, plate-like crystals were obtained. The crystals were insoluble in concentrated sulfuric acid. The pure crystals had a melting point of 68° C. The substance was characterized as the hydrocarbon, hentriacontane.[19]

The soap solution was evaporated to a small volume and the fatty acids freed by treating with dilute sulfuric acid. The fatty acids were removed mechanically, and washed with distilled water. The aqueous-acid portion was extracted with ether to remove any trace of fatty acids. The weight of fatty acids recovered was 1267 grams. This corresponds to 95.33 per cent. of the oil used.

The aqueous-acid fraction was neutralized to litmus paper with sodium carbonate. The solution was slowly evaporated on a steam plate, and the sodium sulfate filtered off by suction. The filtrate was boiled with animal charcoal to remove the red coloring matter. The filtrate was evaporated to a viscous condition. This material was

repeatedly extracted with a solution of three parts of alcohol and one part of ether. The solvent was removed by evaporation. The residue weighed 37 grams. This corresponds to 2.74 per cent. of the oil used. A small portion of the liquid was treated with benzoyl chloride, forming a derivative with a melting point of 72° C., which is the melting point of glyceryl tribenzoate.[20] The liquid was characterized as glycerol.

The crude fatty acids were quite viscous and were brownish-black in color. The neutralization value was 194.05 and the iodine value was 97.5.

The solid and liquid fatty acids were separated by the lead-ether method of Gusserow [21] and Varrentrap.[22] One thousand grams of fatty acids were converted into a lead soap which was refluxed with ether to dissolve out the liquid acid soap. Some loss of both fractions occurred due to the large volume of lead soap formed. The ether soluble lead soap was treated with hot hydrochloric acid to free the fatty acids. The crude liquid acids were black in color. The iodine value of the fatty acid mixture was 113.2 and the neutralization value was 189.3.

The liquid acids, in ethereal solution, were placed in a flask immersed in a freezing mixture. The flask was covered to exclude light. The temperature of the acid-ether solution was brought to —5° C. A solution of 1:1 bromine and glacial acetic acid was added dropwise from a burette to the cold solution, until an excess of bromine was present. The brominated mixture was allowed to stand over night at 5° C. No ether insoluble crystals formed.

The bromide mixture was washed with sodium thiosulfate solution and water to remove bromine and impurities. The ether was removed by evaporation. The bromide mixture was refluxed with petroleum ether for 30 minutes and allowed to stand at 5° C. for 5 hours. A quantity of crystals formed and were filtered off. They were repeatedly recrystallized from xylene. The melting point was 114.5° C. Linoleic tetrabromide [18] melts at 114-115° C.

The petroleum-ether solution was evaporated until there was no further loss of weight. A portion of the residue was assayed for bromine by the Stepanow [23] method. The perecentage of bromine found was 35.83. The theoretical value for oleic dibromide [18] is 35.19 per cent.

The liquid acids obtained by the above procedures were characterized as linoleic and oleic acids.

The ether insoluble lead soap was refluxed with HCl and yielded 184 grams of solid fatty acids. The fatty acids were solid at 40° C. and were light yellow in color. The neutralization value was 181, and the iodine number was 27.5.

The methyl esters of the solid fatty acids were prepared by treating an ether solution of the acid with a 3.5 per cent. solution of HCl in methyl alcohol. The solvents were removed by evaporation and the esters washed until neutral. The weight of the esters amounted to 175 grams.

The methyl esters were repeatedly fractionally distilled at a pressure of 1.5 mm. of mercury, until eight fairly well-defined boiling fractions were obtained. Fractions Nos. 3, 4 and 5 were found to be unsaturated to some extent. They were added together and brominated. The brominated mixture was distilled under reduced pressure and the fractions collected as previously noted. By this procedure the methyl oleate was largely removed from the solid acid esters.

Fraction No. 1 was distilled under atmospheric pressure. A small amount of material passed over at 102-103° C. The amount was very small and had the odor of oil of pineapple. These facts indicate the presence of small amounts of n-butyric acid.[20] The remainder of the material passed over at about 315° C. The saponification value of the distillate was 209.5. The theoretical saponification value [24] of methyl palmitate is 207.5. The fatty acid recovered from the ester had a neutralization value of 217.1, and a melting point of 62° C. after being repeatedly recrystallized from alcohol and glacial acetic acid. The theoretical neutralization value [19] of palmitic acid is 218.92. The melting point [18] is 62.62° C. The acid was therefore characterized as palmitic acid. Similarly the acid from Fractions Nos. 2, 3, 4, 5 and 6 was characterized as palmitic acid.

Distillate No. 7 had an average saponification value of 170.7. The theoretical saponification value [25] of methyl arachidate is 171.7. The neutralization value of the recovered acid was 182.3. The theoretical neutralization value [19] of arachidic acid is 179.63. The purified acid, recrystallized from alcohol and glacial acetic acid, melted at 68° C. The values obtained indicate arachidic acid, although the

melting point of arachidic acid is given in the literature as 77° C. No pure arachidic acid could be obtained from the methyl ester.

Distillate No. 8 had a saponification value of 154.1 and the recovered acid had a neutralization value of 154.7, and a melting point of 80° C. The theoretical saponification value [26] of methyl lignocerate is 146.7. The theoretical neutralization value [19] of lignoceric acid is 152.29, and the melting point [18] is 80.5° C. The acid obtained from Distillate No. 8 was therefore characterized as lignoceric acid.

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(24) Calculated from $C_{15}H_{31}COOCH_3$.
(25) Calculated from $C_{19}H_{39}COOCH_3$.
(26) Calculated from $C_{23}H_{47}COOCH_3$.

NEW METHOD FOR IODATION AND CHLORINATION OF VEGETABLE AND ANIMAL OILS

By Frederick R. Greenbaum, D. Sc.
Philadelphia, Pa.

A four step, practical method for the halogenation of vegetable and animal oils is herein described by the Author.

EVER since the introduction of iodized oils by Siccard and Forestier, as a radiopaque substance for the visualization of certain cavities in the body, the use of these radiopaque substances became wide spread and is used today as routine hospital procedure.

The requirements of iodized oils for diagnostic purposes are: low toxicity, high radiopacity and some degree of stability.

The iodized oils available on the market possess these requirements. However, all of these oils on the market cause some degree of irritation, are quite unstable, or turn dark when exposed to light or subjected to even moderate heat. For many purposes their viscosity is not high enough and their taste and flavor is unpleasant. The patients are loath to swallow the oil due to its oleaginous taste. Besides, the price of practically all iodized oils on the market is high.

Iodized fats and iodized oils produce in general the same systemic effect as ordinary inorganic iodides, but their iodine is more slowly absorbed and excreted.

The main use of iodized oils, however, is as contrast mediums in Roentgen diagnosis, especially of tumors of the cord, in the localization of bronchial and pulmonary lesions and in gynecology. Vegetable oils are preferable, as animal oils cause local irriation. According to the method of iodation, the oil may contain iodine alone or iodine and chlorine.

The method that I wish to report herewith will introduce one atom of iodine and one atom of chlorine, in an adjacent position, into the unsaturated linkage of the fatty acids of vegetable or animal oils.

The first step comprises the removal of the free acidity of the vegetable or animal oil. That means the free fatty acids are removed because they are later on very detrimental, frequently causing a darkening of the oil.

This is accomplished by taking 1000 grams of the vegetable or animal oil with about 2000 cc. of denatured alcohol, and then add N/2 sodium hydroxide and a few drops of phenolphthalein, and stir mechanically. The addition of N/2 sodium hydroxide is continued until it imparts a pink color to the alcohol. Should this pink color disappear more N/2 sodium hydroxide is added. The amount of the N/2 sodium hydroxide will depend on the degree of the acidity of the vegetable or animal oil.

The oil is then allowed to settle, the alcohol is syphoned off and two liters of water are added, and stirred for a few minutes. This frees the oil from the alcohol. The oil is allowed to separate and will be floating on top. The water is now syphoned by means of suction. Another two liter portion of water is added to the oil, and stirred again for a few minutes. It is allowed to settle and the water is now syphoned off. To this purified oil, any oil solvent such as chloroform, ethylenedichloride, carbon tetrachloride, or ether may be added. I used technical ether, because it is the lowest boiling solvent and can most easily be removed from the finished product.

The second step comprises the preparation of the iodizing and chlorinating agent in *aqueous solution.*

This is based upon the reaction between potassium iodide, potassium iodate and hydrochloric acid. If an excess of potassium iodide is used over the potassium iodate, the reaction in aqueous solution in the presence of hydrochloric acid will result in free iodine, which is precipitated in accordance with the following equation No. 1:

$$5KI + KIO_3 + 6HCl \rightarrow 6KCl + 3H_2O + \underline{3I_2}$$

However, if a smaller amount of potassium iodide is used, in the presence of a great excess of concentrated hydrochloric acid, iodine monochloride is formed in the status nascendi, which dissolves in the water and hydrochloric acid, forming a clear cherry red aqueous solution as per the following equation No. 2:

$$2KI + KIO_3 + 6HCl \rightarrow 3KCl + 3H_2O + \underline{3ICl}$$

In this form the iodine monochloride is very reactive and will readily yield its iodine and chlorine to any oil with which it is brought into contact.

As an illustration for the preparation of this *aqueous iodine monochloride* the following procedure may be given:

In 720 cc. of distilled water, 357 grams of potassium iodide are dissolved, and 239 grams of potassium iodate are added to this cold

solution; 720 cc. of concentrated hydrochloric acid (U. S. P.) are added with mechanical vigorous stirring in one rapid stream. The solution gets rather warm, 50°-60° C. A dark precipitate of iodine monochloride is first formed, which on continued stirring will go in solution. The stirring should be continued until the solution has a dark reddish orange color, and is absolutely clear. This iodizing and chlorinating solution is cooled to 15° C., and is now ready for use. It is a strongly acid solution of iodine monochloride, which acts upon the oil introducing the iodine as well as the chlorine.

The third step comprises the actual introduction of the iodine and chlorine into the purified oil by means of this aqueous solution of iodine monochloride. This method differs from the ones usually employed that no mercuric chloride is being used as a catalyst and, therefore, the danger of a possible contamination of the iodized oil with mercury is elminated. The Hübl Method for determining iodine in fats and oils used mercuric chloride as a catalyst. By using the above described aqueous iodine monochloride solution no catalyst is necessary.

The iodizing solution is mechanically stirred and well cooled with ice and water. Now, the ether solution of the purified oil is slowly added to the iodizing solution under vigorous stirring. Care should be taken that the temperature remains between 20°-25° C. so as to prevent boiling of the ether. The addition of ether oil solution should be slow, only small portions being added. After all the oil has been added, stirring for about ten minutes will completely iodize the oil. The remaining iodine monochloride solution has lost most of its color and is faintly yellow or almost water white. An assay of this residual solution showed that 99 per cent. of the iodine monochloride was used up by the oil and demonstrates how exhaustively, almost quantitatively, the iodation and chlorination of an oil occurs by this method.

Upon allowing the iodized oil to stand, it will settle to the bottom, as the specific gravity is greater than that of water, and the supernatant aqueous portion is syphoned off, and at this stage 500 cc. of ethylenedichloride are added. Ethylenedichloride is added as an additional solvent, to permit the constant washing with water, as ether possesses a certain solubility in water and would gradually be washed away.

After the 500 cc. of ethylenedichloride have been added, the oil, ether, ethylenedichloride solution is washed in a wide mouth bottle

with constantly running tap water, until all the hydrochloric acid is removed. This can be shown by the addition of a few drops of bromthymol blue, which will give a yellow color when mineral acid is still present, but if all the acid is removed a blue color is obtained. It usually takes several hours.

The fourth step consists in removing any free (uncombined iodine) from the oil and in stabilizing the iodized oil by removing any free fatty acids which may have been produced by the iodation process.

This is accomplished by separating the ethylenedichloride oil solution from the water as completely as possible and by adding 750 cc. of denatured alcohol to it, and stirring mechanically. To this was then added alcoholic sodium hydroxide. This alcoholic sodium hydroxide was prepared by refluxing 500 cc. of denatured alcohol with 20 grams of alkali flakes, cooled when dissolved and filtered at room temperature. The addition of this alcohol sodium hydroxide was carried out until a pink color remained with phenolphthalein. When this is the case, it is then allowed to settle. The alcohol was separated from the oil and was syphoned off. (It may be recovered by distillation.) The iodized oil was then washed with water until the pink color to phenolphthalein disappeared and the wash water has lost its soapy appearance.

Then the oil layer is separated from the water by syphoning, and dried with anhydrous sodium sulphate, treated with activated charcoal, stirred and filtered. The solution should be brilliantly clear, of a light yellow color. Then it is placed into a round flask and the ethylenedichloride and the ether removed by vacuum, at first without heat, which mainly drives off the ether, and then with vigorous aeration, the remainder of the ether is removed. It is now placed in a thermostatically controlled water bath and the temperature is maintained at about 55° C. After about six to eight hours vacuo distillation all of the ethylenedichloride is removed and a nice light yellow viscous iodized and chlorinated oil remains behind.

This chloriodized oil contains one atom of iodine and one atom of chlorine chemically and firmly bound in the position of the unsaturated linkages of the fatty acids contained in the oil.

This iodized oil has great stability against light and heat. The stability may still be further enhanced by the addition of 0.5 per cent. to 1 per cent. of its weight of a purified non-iodized oil, which will absorb any of the iodine which in time may be eliminated.

SUMMARY

A new method for the iodation and chlorination of a vegetable or animal oil is described, consisting of four steps:

First step: The removal of any free fatty acids of a vegetable or animal oil, by treating it with alcohol and N/2 sodium hydroxide.

Second step: Preparation of the iodizing and chlorinating solution, yielding an aqueous solution of iodine monochloride.

Third step: The iodation and chlorination of the vegetable or animal oil in ether solution, by means of the aqueous iodine monochloride.

Fourth step: The removal of free iodine and any free fatty acids or free acidity by means of alcoholic sodium hydroxide.

These four steps will yield an iodized and chlorinated oil of great stability towards heat and light and possessing practically no irritating properties. It seems that the presence of chlorine, firmly bound adjacent to the firmly bound iodine, stabilizes the iodine combination in the oil.

The Infra-red Absorption Spectrum of Vitamin C. D. Williams and L. H. Rogers, *Jour. Amer. Chem. Soc., 59,* 1422 (1937). In order to obtain additional information on the molecular structure of Vitamin C, the authors have made a study of its infra-red absorption spectrum in the region from 2 to 8 μ rather than the previously studied region between 200 and 400 μ. In obtaining the absorption data the transmission of a vitamin solution was compared with the radiation transmitted by a cell of equal thickness containing water. No strictly theoretical interpretation seems possible for the infra-red absorption spectrum of a molecule as complex as Vitamin C but the authors' results thus far seem to be in agreement with the molecular structure suggested by Hawarth and Hirst. From considerations of this structure it appears that there should be six absorption bands in the infra-red region between 2 and 8 μ. These bands have been observed and, in addition, two other bands which may arise from the lactone linkage since each organic radical is known to give rise to a characteristic series of bands. L. J. K.

A STUDY OF STRUTHIOPTERIS SPICANT

By Forest J. Goodrich[1] and Estelle Koozin[2]

That filicin, an active medicinal, is present in one variety of fern, is no warrant that other ferns contain it. This article describes a research which gave such valuable though negative findings.

Introduction

THE ferns of Washington have long attracted attention because of their unusual foliage and ornamental beauty. However, comparatively little work from the standpoint of chemistry, pharmacy and pharmacology has been done with these plants. This investigation of Struthiopteris spicant (Deer Fern) was undertaken to determine whether it is of medicinal value, particularly whether it possessed anthelmintic properties similar to those of the official Aspidium.

Struthiopteris spicant is a tough evergreen fern. The leaf blades are linear to linear oblanceolate, simple but pinnately 1-parted or 1-divided, 15-100 cm. long and grow in a rosette. Microscopical examination of sections of the rhizome reveals bundles which possess both xylem and phloem and may be classified as amphiphloic simphonosteles. The parenchyma, which forms the ground tissue of the rhizome is filled with starch grains.

Chemical

The rhizome and roots were used in the chemical investigation. These were collected near the shores of Lake Washington, near Seattle, in January, April, August and October, 1935. They were air-dried and ground to a No. 20 powder, and this material was used for all analyses except moisture determination which was conducted on fresh samples. All tests were run in duplicate and the following data represents the mean of duplicated results:

Moisture

Seven to ten gram samples dried first at room temperature showed the presence of 66.48 per cent. moisture. The total moisture, after drying at 105 deg. C. was 69.82 per cent.

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[2] Teaching fellow, University of Washington.

Selective Extraction

Nine to ten gram samples were extracted in a Soxhlet extraction apparatus. Eighteen hours were allowed for extraction with each solvent which were used in the order named in Table I below.

TABLE I

SELECTIVE EXTRACTION

Solvent	Per cent. Extractive	
	Dried at room temperature	Dried at 105° C.
1. Petroleum ether	1.7%	1.52%
2. Ethyl ether	0.83%	0.68%
3. Chloroform	0.34%	0.32%
4. Alcohol, 95%		19.16%
5. Water, distilled		10.81%

Ash

Ash content as determined by the U. S. P. X method was 3.08 per cent. total ash, 2.59 per cent. acid soluble and 0.49 per cent. acid insoluble.

Starch

Starch was determined by Hooker's method. This method was chosen in preference to the A. O. A. C. method because it offers a more convenient method of separating the starch from other material present. The results indicated the presence of 7.73 per cent. starch.

Carbohydrates

Hooker's method was used for carbohydrate determination also. The results were 6.50 per cent. total sugars and 3.89 per cent. reducing sugars.

Pentosans

The A. O. A. C. official phloroglucin-hydrochloric acid method indicated the presence of 3.02 per cent. pentosans.

Alkaloids

A fifty gram sample macerated with 300 cc. of 1 per cent. aqueous tartaric acid solution and the extract purified by extraction with a mixture of chloroform and ether gave no indication of the presence of an alkaloid on being tested with several alkaloidal reagents.

Glucosides

Three methods were used in attempting to demonstrate the presence of glucosides in the fern. One involved extraction with 60 per cent. alcohol, concentration under diminished pressure, clarification of the aqueous solution of the resulting residue, and crystallization by spontaneous evaporation. The second method was that of Bourquelot in which the material was extracted with hot alkaline 95 per cent. alcohol, residue after distilling off the alcohol taken up with water, clarified, concentrated under diminished pressure and boiled with acetic ether. In the third method the material was extracted with water, clarified, shaken out with chloroform and solution allowed to concentrate spontaneously. None of the methods gave any indication of the presence of glucosides.

Filicin

The U. S. P. X assay for filicin under oleoresin of Aspidium gave negative results. A confirmatory test, using Kraft's method was conducted and also indicated the absence of filicin.

Toxicity

The alcohol extract of the rhizomes, fed in appreciable quantities to white rats, produced no noticeable untoward effects, indicating lack of toxicity.

Conclusion

The conclusion may be drawn that Struthiopteris spicant cannot possibly be used as a therapeutic agent.

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The Iodination of p-Aminobenzenesulfonamide and Some Symmetrical azobenzenesulfonamides. J. V. Scudi, *Jour. Amer. Chem. Soc., 59,* 1480 (1937). The author studied the preparation of the ortho mono- and diiodo derivatives of p-Aminobenzenesulfonamide in the hope that introduction of this radiopaque element might make it possible to visualize, roentgenologically, the course of this clinically important drug through various parts of the anatomy. Yields ranging from 90 to 100 per cent. of the desired compounds were obtained by the iodine monochloride methods of Kalle and Co. Dismutation of aryl iodine in boiling hydrochloric acid is demonstrated. Iodine in alkaline media is shown to produce azo- and nitrosobenzenesulfonamides, compounds which are of bacteriological interest. No report is included on the bacteriological and roentgenological properties of these substances since the investigation has not as yet been completed.

L. J. K.

Standardization of Tablets for Determining Methylene Blue Reduction in Milk. H. J. Conn, *Amer. Jour. Pub. Health, 27,* 793 (1937). The actual dye content of Danish made tablets has shown a decreasing value since 1920. A new lot analyzed in 1935 was found to contain only 14.6 mgm. per tablet as compared with 30 mgm. per tablet supplied in 1923. The tablets, the bulk of which consisted of sodium chloride, crumbled easily, which was undoubtedly responsible for some of the variation. It has been pointed out that there are serious objections to methylene blue in the form of the chloride which has always been employed, largely because of the difficulty in standardizing the dye itself and in preventing its oxidation into other compounds that do not have the same action when used as an indicator of reduction. It is pointed out that this can be avoided by using methylene blue thiocyanate instead of the chloride. W. G. B.

DETECTION OF COCAINE IN MIXTURES OF COCAINE AND NUPERCAINE

By Charles Milos*

A delicate qualitative test is offered whereby cocaine may be separated and identified when admixed with nupercaine.

IN acid solution cocaine ($C_{17}H_{21}NO_4$) and its salts, on the addition of platinic chloride solution ($H_2Pt\ Cl_6$). gives a feathery crystalline precipitate, which is characteristic for cocaine and may be observed and identified under the microscope. (Stephensen Microchemical Tests for Alkaloids. Lippincott, 1921.)

When nupercaine, the hydrochloride of Butyloxycinchonnic Acid Dimethylendiamide, is present the positive identification of cocaine becomes difficult. In acid solution nupercaine on the addition of platinic chloride solution gives an amorphous precipitate which gradually becomes crystalline on standing. Mixtures containing nupercaine in small amounts alter the characteristic crystal formed by cocaine with platinic chloride beyond positive identification and those containing nupercaine in substantial amounts prevent their formation or entirely mask them from view. In order to identify cocaine in the presence of nupercaine a separation of the two components is necessary, after which cocaine can be identified by the formation of characteristic crystals with platinic chloride or other alkaloid precipitants. (C. C. Fulton, *American Journal of Pharmacy*, 105, 326-339, 374-380, 1933.)

A method of separation was worked out, which takes advantage of the fact that the free base of nupercaine is precipitated in an ammoniacal solution and is but slightly soluble in water. Sufficient cocaine dissolves to allow for its extraction and identification. The last traces of free base of nupercaine are removed by adjusting the pH to 1.8 and extracting with a suitable solvent, leaving the cocaine in solution.

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Preparation of Standard Solutions

0.2 Normal Potassium chloride. Dissolve 7.456 grams of C. P. potassium chloride in 200 cc. of distilled water and make up to a volume of 500 cc. with distilled water.

0.2 Normal Hydrochloric acid. Take 100 cc. of a normal hydrochloric acid solution and dilute to a volume of 500 cc. with distilled water. Ten cubic centimeters of this solution should require 20 cc. of 0.1 N sodium hydroxide for neutralization, using methyl orange as indicator.

Method

Take 0.15 grams to 0.2 grams of sample and dissolve it in 10 cc. of N/10 hydrochloric acid. Transfer to a separator and make alkaline with ammonium hydroxide, and add an excess of four to six drops. Shake vigorously and continue the agitation until the precipitate first formed settles out leaving the solution clear. Filter into another separator, wash the precipitate twice with 5 cc. of water made alkaline with a few drops of ammonium hydroxide. If the filtrate is not clear, re-filter, and shake out three times with petroleum ether, using thirty cubic centimeter portions. Collect the petroleum ether in a separator, wash it with 5 cc. of water, discard the water, and evaporate off the petroleum ether in a dish over a steam bath, using a fan.

Dissolve the residue in 10 cubic centimeters of solution, made by mixing 10 cc. of 0.2 N hydrochloric acid with 75 cc. of 0.2 N potassium chloride. Transfer to a separator and extract with chloroform containing 10 per cent. by volume of 95 per cent. ethyl alcohol, using 30, 20, 10, 10 and 5 cubic centimeter portions. Discard the chloroform. Now extract once with 50 cc. of petroleum ether. Wash the petroleum ether with 2 cc. of water. Add the water to the buffered solution and discard the petroleum ether. Add ammonium hydroxide to the buffered solution until the solution is basic to litmus, one to two drops being generally sufficient, and shake out twice with petroleum ether, using 25 cc. portions. Take the combined petroleum ether and wash it with 5 cc. of water, discard the water, and filter the petroleum ether into a dish and evaporate off over a steam bath, using a fan.

Dissolve the residue in a drop or two of dilute sulphuric acid. Transfer to a slide and add a drop of platinic chloride solution. If cocaine is present its characteristic crystals with platinic chloride will be observed under the microscope.

Summary

1. A method is given for the separation and identification of cocaine in the presence of nupercaine.

2. One milligram in 100 milligrams of nupercaine can be readily detected by this method of separation.

3. The method will not give quantitative results, and can be used only for a qualitative identification of cocaine.

4. The molecular structure of the cocaine is not altered in any way by this method of separation.

The author expresses his appreciation for facilities placed at his disposal by George W. Romig, Jr., Chemist in Charge of the New York Laboratory.

The Determination of Lead Peroxide. J. N. Mrgudich and G. L. Clark, *J. Ind. and Eng. Chem.,* Anal. Ed., *9,* 256 (1937). The purpose of this investigation is an attempt to select from the most common procedures the one which seems to yield the most accurate results. To this end a given sample of lead peroxide was analyzed by each of several methods, the accepted procedures being followed rigorously. In addition certain methods were modified as seemed desirable to the authors. The Bunsen method depends upon the liberation of chlorine upon solution of the sample in hot hydrochloric acid, the chlorine led into potassium iodide, iodine being liberated and titrated. The method gave low results; a modification of it gave higher results, but was found cumbersome and slow. The Diehl method, which measures the iodine liberated when the sample is dissolved in potassium iodide solution, containing acetic acid and sodium acetate, is recommended as reliable. The Schaeffer method, in which the sample is dissolved in hydrogen-peroxide and nitric acid, was found to be unreliable, the results being low and widely different. The Lux method, which directs solution of the sample with oxalic and nitric acids, and titration of excess oxalic acid with permanganate, was next investigated. As originally described, the method is unreliable, due to decomposition of oxalic acid by nitric acid. The authors recommend a modification of the Lux method, replacing nitric with perchloric acid, permanganate with ceric sulfate, and observing the end point with an electron beam sectrometer. L. A. R.

ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

Bacteriology . . . . Louis Gershenfeld, B. Sc., Ph M.
Biochemistry, Nutrition, etc. . . . Arno Viehoever, Ph. D.
Biology . . . . . Marin S. Dunn, Ph. D.
Chemistry . . . . . Arthur Osol, Ph. D.
Pharmacy . . . . . E. Fullerton Cook, Ph. M.
and their assistants

THE TREATMENT OF IRON-RESPONSIVE ANEMIA WITH IRON ASCORBINATE, AND CONTRIBUTIONS TO THE MECHANISM OF THE EFFECT OF IRON AND TO THE IRON DEFICIENCY DISEASE PROBLEM

By Ludwig Heilmeyer, Jena*

The so-called iron-responsive anemias attract daily more and more attention from a clinical and pathophysiological point of view. Anemia research has shown that these forms of anemia are differentiated by means of two special characteristics from the large group of secondary anemias. First, through their excellent response to administration of iron and through morphological criteria consisting in the lowering of all indices including the dyeing index, of the cell diameter, the cell volume, and the hemoglobin increase. Small erythrocytes with little hemoglobin are formed. Perhaps there is also found a serum particularly low in pigment and almost water clear. These characteristics are encountered most pronouncedly in the chronic blood anemia, especially in long drawn out ulcus bleeding and in the so-called achylic chlorine anemia (Knud Faber (3), Kaznelson (7)), that more recent anemia picture found prevalent in women from 30-60 years of age, and almost always in combination with the lack of acid in the gastric juices. To this group belong also such anemias found in persons who had stomach operations, especially after extensive removals, or in badly functioning gastroenterostomia, in intestinal diseases accom-

*From the Medical Clinic of the University of Jena, Germany. Translated by **Dr. Arno Viehoever.** *Deutches Archiv Fur Klinische Medizin,* Vol. 179, pages 216-231 (1937).

panied with disturbances of the resorption and in degraded, undernourished people such as vagrants. The same picture of anemia was also observed in worm diseases, particularly in carriers of ankylostomum duodenale caused not only by special worm toxins but—according to W. O. Cruz (2)—the continued small losses of blood and the nutritional disturbances produced by the parasites.

In severe and long continued cases of these anemias, most markedly but not exclusively in the achylic chlorine anemia, also other symptoms are observed having nothing directly to do with the lowering of hemoglobin, as atrophic disturbances in nails and hair, changes of skin and mucous membranes, especially of tongue, influences discussed later in this treatise.

The therapy of this anemia consisted in administering iron in as great amounts as possible, since Naegeli's (8) remarkable effect of ferrum reductum is known. The doses have now been increased up to 10 gm. daily. One observes indeed, an excellent regeneration. Hemoglobin is increased as well as erythrocytes and in the beginning there occurs perhaps a reticulocytes crisis. In the course of treatment the cell forms approach the normal. The one who has carried out this treatment frequently, observes, however, again and again, cases in which the ferrum reductum therapy cannot be administered on account of gastro-intestinal disturbances. On account of vomiting, diarrhea, gastro-intestinal pains, loss of appetite, feeling of sickness, the patients refuse to take the medicine. This is the more rational, as very often severe intestinal trouble exists even before the treatment. One may select other iron preparations without complete satisfaction. Either they do not agree well with the patient or the anemia is not improved. In such cases the desire exists for injectable iron preparation of absolutely certain effect. Starting with the conception of Starkenstein, that the effect of iron is essentially due to the ferrous iron, experiments have been carried on with Wickler in this sense, using ferrous chloride and ferrous sulphate with marked success. As the solutions employed are not stable, they must be freshly prepared. Also sometimes injuries occur to the venus wall with thromboses. We endeavored, therefore, to combine the iron, if possible, with a physiological substance in a 2-valent form which lowers its irritating effect upon the tissue and, if possible, exerts simultaneously a favorable effect upon blood formation. Vitamin C, ascorbic acid, fulfills these requirements excellently. Dr. Maurer, having

worked on the synthesis of ascorbic acid, upon the author's suggestion, prepared the complex salt of the 2-valent iron with both ascorbic acid and iso-ascorbic acid. The blue complex salt is water soluble with neutral reaction. The ink blue solution becomes colorless even in weakly acid environment. In the atmosphere the complex is slowly oxidized so that the solutions must be kept away from the air. In the course of one year's experience the iron salts of both ascorbic acid as well as iso-ascorbic acid proved of equal value for the iron therapy. This is explained by the fact that through partial oxidation in the preparation of the complex salts, spacial differences of the isomeric acids are largely removed. Maurer and Schiedt (*Biochem. Z. 67,* 285 (1936)) have elsewhere discussed the chemical part of these new compounds. For therapeutic purposes iron ascorbinate is now manufactured by the Nordmark Werken of Hamburg.

For the suitable concentration for intravenous injections 10 mg. of iron were dissolved in 1 cc. In all cases these injections were taken without discomfort, usually injections were given daily, once, sometimes twice in 1 cc. quantities. During the injection there occurs a slight sensation of warmth or heat similar to the injections of calcium solutions. Sometimes one sees also slight vasomotoric symptoms in the face with dilation of the veins. These symptoms are the less marked the more severe the anemia. Even after daily adminstration, prolonged for a week, no other harmful side effects were observed. Local injury was not observed when faultless injection technique was used; in paravenous injection, easily curable, infiltrates occur. In sensitive persons, sometimes after treatment for weeks, slight thromboses occur. Almost exclusively iron-responsive anemias were treated.

Discussion of Results.

The intravenous injection of 10 mg. daily of iron ascorbinate in all cases, even the severest, caused an increase of the Hb values and erythrocyte values. The magnitude of increase varied from .7 to 1.7 Hb per cent. per day, and amounted in the average to 1.3 Hb per cent. On sufficiently prolonged treatment normal values were reached. Generally, the increase of cell number always precedes the increase of the Hb content. The effect of iron mentioned appears, on first sight, surprising if one considers that in ordinary oral medication of ferrum reductum one hundred to one thousand times the

amount is necessary to obtain the same results. It is known that the largest amount of perorally administered iron occurs again in the feces. If one may draw a conclusion from the effect upon the degree of resorption of iron, the intravenously introduced quantities would about correspond to the amount of resorbed iron. Heath, Strauss, and Castle (5) have already made similar observations. In their studies 1000 mgm. perorally administered iron, per day, had about the same effect as 32 mgm. of iron citrate given parenterally. However, they have found the last form of application toxic, so that they prefer the peroral medication. Sonnefeld (12) administered Siderophen, an organic iron preparation, intramuscularly, 10 mgm. per day, and observed an increase of Hb and erythrocyte values.

The therapeutic significance of the intravenous administration of iron doubtless lies in the fact that it is possible to cure severe iron-responsive anemia where severe gastro-intestinal disturbances make peroral administration of iron very difficult, if not impossible.

Further significance of the parenteral iron therapy lies in its increased irritating action, resulting in the fact that perorally administered iron, under the influence of preceding or succeeding peroral doses, has a better effect than otherwise. Thus, case No. 14 showed a surprising, rapid, and marked effect of perorally administered iron after intravenous pre-treatment. Reversely, in cases 12 and 13, after preceding intravenous injection following an acute active or inactive peroral therapy an enormous increase of blood values was observed, even after very small doses. The increased irritating effect of intravenous doses is apparent also in the fact that frequently the cell number shows a greater increase than the Hb content. Thus, in the future one should apply the parenteral iron therapy, even in such cases in which the peroral administration shows no effect at all, or one should combine both methods.

The experiments with peroral application of the iron ascorbinate have shown that even very small amounts of iron exert a marked effect. Doses of 300 to 600 mgm. daily of iron, as case No. 9 showed, caused a very rapid *restutio ad integrum* in a very severe anemia, which had been previously treated without success with other iron preparations. In addition to the effect on the blood formation, we also see in our case certain general effects, as increase in body vitality, increase of the emotional functions, increase of appetite and weight, and increase of resistance to infections. In a single case, of course,

it is difficult to decide how far the effect is due to the administration of iron ascorbinate or other therapeutical measures. The following considerations aim to show that in the genuine deficiency of iron, upon addition of iron, general effects are released in addition to the effects on the blood.

Mechanism of the Effect of Iron—The Existence of an Iron Deficiency Disease?

Our observations permit some consideration concerning the mechanism of iron effect. These questions are still under discussion and particularly in the modern time under the influence of clinical observations the problems of iron-responsive anemia have come to the foreground of interest. While many authors see in these anemia cases a material effect of iron when an iron deficiency is present, Naegeli recently has fostered the irritation theory. The recent studies of Wichels and Hoefer and our own observations, after parenteral administration of iron, have shown that iron doubtless has an irritating effect on the bone marrow, even in healthy people. Some time after the iron injection one sees a marked increase of reticulocytes in the peripheral blood, lasting for a short time, which must be explained as a result of the irritating effect upon the bone marrow. This irritating effect is, however, unspecific, as it is also obtained after administration of different vitamins, (according to Seyderhelm (11)) after irritation in the central nervous system (Ginzberg and Heilmeyer (4)), and after other methods of medication.

With these determinations of a short lasting irritating effect, not much can be done for the explanation of the clinical action of iron, for the basic question presents itself—whether in iron-responsive anemia a lack of iron really prevails. While many investigators accept that opinion, not a single certain proof exists for it. We are now occupied in numerous studies to obtain a clarification of this problem concerning the iron metabolism in such patients. The observations are not terminated, but some results point to the existence of a deficiency of iron. Thus, we have found, together with Ploetner, in cases of microcytary anemia frequently an enormous decrease of the freely circulating iron of the serum. From a purely clinical point of view the acceptance of a deficiency disease suggests itself. In this connection the numerous side symptoms observed in such cases are of interest. The marked fatigue and adynamia were not ob-

served to the same extent in other forms of anemia (see case 8). Changes in the nail occurred showing the hollow nail formation and fracture of the nail; also change of the hair growth, straggly dry hair, especially thin hair; and following these symptoms occurred inflammation and atrophy of the mucous membrane of the tongue and throat, paræsthesis, and disturbance of the menstruation. In this connection M. P. Schmidt observed first, experimentally, the accompanying symptoms of the state of iron deficiency. He found exactly the same changes in the appendage formations of the skin. The mice of the third generation, lacking iron, showed a sparse and slow growth of hair, straggly fur, and frequently naked spots in the fur. He describes the loss of vital power of these animals as follows: When running, they ramble and wobble frequently and often become too weak to reach the site of their usual fodder dishes. In addition he observed a very marked general inhibition of growth of the young animals. All of these symptoms receded under administration of iron. We could observe, clinically, the same results. The disappearance of adynamia upon intravenous application of iron occurs much more rapidly than the increase of values of hemoglobin. One has the impression that the application of iron acts like the administration of lacking vitamins. One must remember, for the explanation of this observation, that iron occurs in the organisms not only as a building stone of hemoglobin, but that many important ferments and cell catalysts are iron-containing substances as for instance cytochrom, catalase, oxydase, and peroxydase, and especially the respiratory ferment of Warburg. Should not these substances undergo a change in metabolism similar to hemoglobin and the other body cells reach a state of want of ferment? This is probably for the continuously replaced cells, as epithelia of mucous membranes, for the cells of the outer epidermis and formations attached to them. Thus we have an explanation for the fact that deficiency in iron is especially noticeable in the replaceable organs, such as blood, skin, hair, nails and mucous membranes.

From this point of view the iron responsive forms of anemia present a uniform picture of disease, representing an avitaminosis where the lacking vitamin actually is represented by iron. The next problem is the cause of the iron deficiency. Our material gives some information which agrees with the opinions expressed in literature.

Theoretically, iron deficiency originated first with losses of iron externally, secondly through diminished introduction of iron, thirdly through diminished resorption from the intestinal canal, fourthly through disturbance of the intermediary metabolism of iron. Marked losses of iron externally are present in our cases, as a result of large losses of blood (cases 1, 2, 7, 9, 10 and 13). The diminished application of iron through food occurs in case No. 3, a very badly nourished vagrant. In cases 4, 6, 7, 10, 12, an ulcus diet was administered. This latter diet is extremely poor in iron. While a healthy person in iron balance excretes daily between 20 and 40 mgm. of iron and takes in about the same amount of iron, the excretion of iron after the ulcus diet sinks to 5-10 mgm. per day (according to Heilmeyer and Schadt (6)). These small amounts of iron do not suffice for the replacement of the large losses of iron.

Many investigators have made anacidity and disturbance of digestion responsible for decreased resorption of iron. Indeed even after our observations, the extremely important factor is evident here. Cases 1, 3, 4, 6, 8, 9, 12 and 14 show anacidity or subacidity. Unfortunately three cases were not investigated in connection with conditions of gastric acidity. Furthermore, in all cases gastritis of different degrees were found upon X-ray examination. Without exception we observed always two or even three factors which are active in the sense of iron deficiency and come together in an individual case, so that they furnish certain support for the assumption of a deficiency disease. One should not forget that in disturbances of resorption and decreased iron availability the physiological blood losses of the female, through menstruation, may become of significance for the formation of an iron deficiency condition. Thus, possibly, the much more prevalent conditions of iron deficiency anemia in the female than in the male sex phase may be explained.

Our observations also permit some expressions concerning quantitative relations of iron assimilation. In case 2 the increase of hemoglobin during the treatment amounted to 44 per cent. That corresponds to an increase of total hemoglobin to 500 gm. and of an increase of about 220 Hb while the total amount of blood remained approximately the same. This result was obtained through injection

of 310 mgm. of iron. This amount of iron, however, only sufficed for the formation of about 93 gm. of Hb. Similar conditions prevail in case 4. Using the same calculation two injections of 140 mgm. of iron, 100 gm. of hemoglobin were newly formed, although these 140 gm. of iron only sufficed for the formation of about 52 gm. of Hb. The same applies to cases 7 and 8. In case 7 the actual amount of Hb formed, according to our calculation, was 170 gm., the amount obtained from the introduced iron was only 111 gm. In case 8 the corresponding amounts were 125 gm. and 84 gm. In all cases the actual Hb addition is markedly lower than corresponds to the injected amount of iron. We assume, in these calculations, that the actual Hb increase is probably much greater. This shows that the introduced iron not only accounts as a building stone, but that it stimulates, obviously, the utilization of food iron and storage iron. One should therefore assume that the organism, in case of iron deficiency, falls into a circulus vitiosus, in which the absorption or utilization of food, or storage iron through the cell is reduced.

An example of how this circulus vitiosus may come about may be observed in the behavior of gastric glands in case 9. The subacidity causes decreased iron resorption. Under the influence of this iron deficiency the function of the stomach glands stops altogether, causing in turn a further lowering of the iron resorption. Through the administration of new iron in the form of a medication this faulty cycle is interrupted, the function of the gastric glands is again set in motion, improving the resorption of iron. Similar relations may prevail in other cells. Thus one may come to the conviction that neither the irritation theory nor the material theory of iron effect has the only significance, but that the changing interaction of both processes prevails.

Finally we consider the process of the formation of erythrocytes in the bone marrow. We know that the iron responsive anemia causes the formation of morphologically different and frequently distorted cells. The cell volume and cell diameter are decreased and the size of cells is not uniform. Through studies of blood replacement in these anemias, carried through by myself and Chang, we showed that the cells formed were not only morphologically, but biologically inferior. The following table explains this.*

EFFECT ON CELLS BEFORE AND AFTER FE ADMINISTRATION

Case	Amount of Blood in Liters	Amount of Erythro-cytes in Millions	Hemo-globin in Grams	Total hemo-globin in Grams	Reticulo-cytes in o/oo	Urine pigments F x M	Urobilin in feces and in urine in mgm. per day	U. M. J.
7								
Before treatment	3,74	1,4	3,6	135	51	6,5	54,6	40,4
After continued Fe administration	4,5	3,0	5,5	242	29	4,2	39,1	16,1
8								
Before treatment	3,3	1,3	1,93	64	18	10,9	47	73,3
After 14 days of Fe administration	3,3	2,2	3,98	130	53 (Crisis)	6,6	78,7	60,5
9								
Before treatment	3,7	3,3	4,37	164	15	6,3	87,6	53,4
After 7 weeks of Fe administration	4,4	5,15	13	570	5	..	34,2	6,0

*For methods see Heilmeyer, *ibid.* 171, 123 (1931).

In all three cases the replacement index is increased twice or four times in comparison to the normal, that is, the erythrocytes formed in the bone marrow are biologically inferior, the life duration in the stream of blood is markedly shortened, they succumb much more rapidly than normal cells to hemolysis. Under iron treatment marked change occurs in all three cases. The replacement index is lowered and upon duration of iron administration returns to the normal (case 7) and even subnormal values (case 9). The last result is the consequence of the complete renewal of blood through healthy cells, occurring in a relatively short time, so that the destruction of the erythrocytes, even in the normal duration of life of the cells formed, must fall to subnormal values. The decrease of replacement also becomes evident from the study of the values of urine pigment, which become lower under the influence of iron therapy. Especially impressive is the effect of iron therapy upon the iron replacement in case 9. The urobilin values decrease very markedly under the influence of iron treatment, even though the amount of circulating blood and the amount of hemoglobin is strongly increased. Joint experiments with Chang have shown that the biological evaluation of erythrocytes in iron responsive anemia goes parallel to a very great extent with the morphological behavior of the cells. In all cases in which we could observe in bleeding anemia and achylic chlorine anemia an increased microcytosis and decrease of volume, the replacement was increased. If the cell diameter and the cell volume were not markedly changed from the normal, then the extent of replacement was also normal.

We also see the same improvement in cells under the influence of iron treatment in the appendage formations of the skin. Thus in cases 9 and 14, after a half year of treatment with iron we could observe a marked improvement of nail growth in a qualitative sense. Another patient reported that since he had been treated with a large amount of iron a marked improvement of the growth of hair was noted.

Reimann (9) and others have pointed out that in iron responsive anemia similar to pernicious anemia there exists in the bone marrow instead of the fat marrow a hypertrophic red marrow containing numerous immature erythroblasts, while the periphery shows only inferior regeneration and a decrease in cells. Thus one can speak of this anemia, similar as in Morbus Biermer of disturbances in the maturity of the bone marrow, or of an arrest in bone marrow forma-

tion. Characteristic for such disturbances in maturing, also expressed in the periphery, is the occurrence of abnormal immature formation of reticulocytes in the streaming blood, described by Heilmeyer (6) in pernicious anemia. We can observe the same in case No. 8. In spite of a relatively small total number of 26 o/oo we find abnormally youthful forms of groups 1 and 2, while the physiological regeneration form of group 4 amounts to less than half. Under the influence of iron this disturbance of maturing is suddenly removed and the youthful cells are thrown in large masses into the blood stream. This results in the crisis of reticulocytes (see Fig. 1). Such behavior is, however, observed mostly only in severe anemias, which are treated with large doses of iron. In milder cases such a marked increase of reticulocytes is not observed.

The similarity of the pathogenetic processes, the disturbance in maturing, in the bone marrow, the formation of biologically inferior cells and the increase thereby produced of the blood disintegration in iron-responsive anemias in pernicious anemia with added disturbances in other organs, is so great that one may well also conclude from this analogy as to the etiology. One may thus come to the opinion that in both forms of anemia a deficiency occurs where in one iron is absent, in the other the Castle Ferment. The disturbance in the Morbus Biermer is, quantitatively, much more severe as far as the cessation of bone marrow formation, as well as the increase of blood disintegration is concerned. Under administration of the needed agent, the disturbance of maturing in the bone marrow as well as the increased hemolysis is removed through formation of biologically superior cells.

Summary

1. With the small amount of 10 mgm. of iron, intravenously injected as iron ascorbinate, one may obtain a full therapeutic effect in iron responsive anemia. This therapy is indicated in all cases in which the peroral iron medication encounters difficulty on account of intestinal disturbances. Even perorally administered iron ascorbinate is evidently more readily resorbed than other iron preparations, as one may observe a full effect of iron with 300-600 mgm. daily.

2. The problem of the mechanism of the effect of iron is taken up as the basis of these studies. It is shown that while iron exerts an unspecific effect of irritation upon the bone marrow, that in iron re-

sponsive anemia most probably a genuine lack of iron prevails. Quantitative experiments are under way on iron metabolism and iron content of bone juices in this anemia. Accompanying symptoms of this anemia are trophic disturbances of the skin, the hair, the nails; the severe adynamia of these patients coincides strikingly with the disturbances observed in iron deficient mice by M. B. Schmidt. These disturbances receded under iron treatment, according to the clinical symptoms observed in man.

3. The cases observed showed at least two, frequently three, factors simultaneously responsive for the occurrence of anemia. The factors are: external iron losses through blood, availability of food lacking in iron (ulcus diet), and disturbances of the digestive system, particularly anacidity of the gastric juice.

4. Intravenously treated cases permit a judgment concerning the quantitative relations of the utilization of the introduced iron. The fact was ascertained that in all cases more hemoglobin was formed than corresponds to the intravenous introduction of iron. The iron thus acts not only as a building stone but also as a stimulant for the better utilization of food iron and storage iron. Under iron deficiency, obviously a faulty cycle occurs, lowering the absorption and utilization of available and deposited iron by the cell.

5. Under the influence of iron deficiency biologically inferior cells are formed as the study of the blood replacement relations in iron deficient anemia indicates. The replacement is increased in four cases, two to four times over the normal. Under iron treatment there is a return to or under the normal. In the bone marrow simultaneously occurs a disturbance of maturing, which is removed suddenly under iron therapy, so that sometimes a crisis of reticulocytes occurs. In connection with this disturbance of maturing of the bone marrow and in connection with the replacement relations in the iron responsive anemia there exists a similar mechanism as in Morbus Biermer; only that in the latter case the process proceeds with a different morphological picture and to a quantitatively increased degree. The similarity in the pathogenetic development of these two anemia forms provides a further support for the belief of a genuine condition of deficiency in iron responsive anemia.

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pH Properties of Colloidal Carbon. B. Wiegand, *J. Ind. and Eng. Chem.*, Anal. Ed., *29*, No. 8 (1937). The pH properties of a series of colloidal carbon samples have been determined by means of a glass electrode system. The pH values so obtained were found to vary over a considerable range (2.6 to 9.3) depending upon the source and method of preparation of the carbon. In an attempt to correlate the pH with other properties of the carbon, an investigation was made of the effect on pH of heating in absence of air. It was found that heating caused an increase in pH. Content of volatile matter was correlated with pH, and it was shown that the higher the percentage of volatile matter, the lower the pH. Finally a study was made of the diphenylguanidine adsorption values of the carbons and these were related to the pH. The author believes that the relation of percentage volatile matter and pH offers the solution to the problem. He feels the pH values observed are not due to actual water soluble acid (or base) but result from selective adsorption of acid or base from the solution. The importance of pH in the choice of the proper carbon for various industrial uses is discussed.

L. A. R.

RECENT REPORTS ON PNEUMONIA AND THE PNEUMOCOCCUS

By Louis Gershenfeld, Ph. M., B. Sc., P. D.

In the May (1937) issue of this Journal (pages 254 and 255), the writer presented abstracts on the use of type specific antipneumococcus rabbit serum as a more efficient therapeutic agent than specific sera from other animals in the treatment of lobar pneumonia. In the July (1937) issue in a review on sulphanilamide and related compounds, abstracts were presented which revealed the use of these chemicals either by themselves or combined with serum therapy in type I and type III pneumococcus infections. Additional experimental work has appeared which tends to prove the efficacy of sulfanilamide in type III pneumococcus infections.

The classification of pneumococci into three fixed types, designated as I, II and III, and a miscellaneous group IV was widely accepted and has been in use for a period of time covering almost one-quarter of a century. For many years group IV was regarded as consisting of pneumococci which, because of their heterogeneity, appeared to be unclassifiable by immunological methods. Subsequent investigations resulted in the extension of the serological differentiation of group IV and twenty-nine additional types were classified as being in this heterogeneous group. At present, thirty-three types of pneumococci, designated as types I to XXXII, are recognized. In the treatment of pneumonia, favorable results have been reported by various drugs, including dyes and quinine compounds, serum, diathermy, and other therapeutic measures. It has been recognized for some time that success with serum treatment depends upon an early diagnosis and the immediate use of specific type serum. Though it has been difficult to assess the value of serum therapy in pneumonia, most observers agree that type I serum is beneficial. Others have reported good results in the specific treatment of type II pneumonia. Some states are supplying serum for use in type I and type II cases. More recently favorable reports have been presented on the use of specific sera in the treatment of pneumococcus pneumonia among types IV to XXXII and in particular for types V, VI, VII, VIII, IX and XIV.

Treatment with specific type serum has resulted in the necessity of typing all pneumonia cases. Many techniques have been introduced for typing pneumonia sputum, but the Neufeld (Quellen) method

has been widely acclaimed because of its simplicity and ease in obtaining a quick report. In this method, a loopful of the sputum is mixed separately with an equal amount of each of the specific type serums (rabbit). After two or three minutes they are examined. When the organism is the same type as the serum, the capsule of the pneumococcus swells to several times its usual thickness, thereby identifying the type.

The pneumococcus is an encapsulated bacterium. In this capsule of the pneumococcus, there has been found complex polysaccharides. The chief polysaccharide of each type of pneumococcus is chemically distinct. Considerable data has been reported concerning these polysaccharides. Finally, investigators are still working and hopeful of obtaining a vaccine or extract of the pneumococcus with which they are experimenting so as to make available a prophylactic agent against lobar pneumonia. A summary of the progress of investigations for the past year along the lines stated above is presented.

Serum Therapy in Pneumonia

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curred in varying proportion from month to month. The pneumococcus pneumonias were subject to treatment by specific therapy which depended upon the reliability of sputum typing. By the use of large doses of serum early in the disease, lives might be saved, the disease shortened, and complications will be reduced to a minimum.

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Standardization of Antipneumococcus Horse Sera and Its Concentrates. L. D. Felton and H. J. Stahl, *U. S. Treas. Dept., Public Health Service, Natl. Inst. Health Bull.* No. 169 (February, 1937). The literature on the standardization of pneumonia sera is reviewed from 1897 to the present. The antibody present measured by the amount of specific polysaccharide (SSS) with which it combines compares with the mouse protection test, and is recommended for the titration of antipneumococcus serum.

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Studies on the Immunizing Substances in Pneumococci. 5. *The Effect of Alkalies on the Immunizing Properties of a Type I Pneumococcus Polysaccharide.* L. D. Felton and B. Prescott, *Bull. Johns Hopkins Hosp. 59,* 114 (1936).

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Oil Aspiration Pneumonia. Report of Two Autopsied Cases in Adults. G. H. Fetterman, *J. Lab. Clin. Med. 22,* 619 (1937). A report is given of two autopsied cases of oil aspiration pneumonia, in which mineral oil was used as a laxative. Mineral oil as a laxative

should be employed only for those in whom there is no interference with the act of swallowing.

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The Distribution in the Blood and Lymph of Pneumococcus Type II Injected Intravenously in Rabbits, and the Effect of Treatment with Specific Antiserum on the Infection of the Lymph. M. E. Field, M. F. Shaffer, J. F. Enders and C. K. Drinker, *J. Exptl. Med. 65,* 469 (1937).

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The Protective Action of Type I Antipneumococcus Serum in Mice. IV. *The Prozone.* K. Goodner and F. L. Horsfall, *J. Exptl. Med. 64,* 369 (1936).

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The Protective Action of Type I Antipneumococcus Serum in Mice. The Effect of Added Lipids on the Protective Mechanism. K. Goodner and F. L. Horsfall, *J. Exptl. Med. 64,* 377 (1936).

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Hemolytic and Combining Capacities of Pneumococci Extracts. W. S. Hull, *J. Immunol. 31,* 37 (1936). The combining power of pneumococcic extracts prepared from nine different strains of pneumococcus remains constant over a long period of time. There is, however, a gradual decrease in the ability to hemolyze red blood cells.

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Serum Typing to Discover the Type of Pneumococcus Causing Pneumonia. W. H. Park, *Preventive Med. 7,* 39 (1937).

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Pneumonia Following the Aspiration of Oils. H. G. Reineke and J. E. Whiteleather, *J. Med. 17,* 344 (1936).

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The Mechanism of a Hitherto Unexplained Form of Native Immunity to the Type III Pneumococcus. A. R. Rich and C. M. McKee, *Bull. Johns Hopkins Hosp. 59,* 171 (1936).

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Fluctuations in Type II Pneumococcus Antibody During the Menstrual Cycle. V. Rose and L. R. Peizer, *Proc. Soc. Exptl. Biol. Med. 35,* 432 (1936).

Precipitation with Antiserum as a Means of Estimating the Immunizing Value of Solutions of Pneumococcus Oral Vaccines. V. Ross and L. R. Peizer, *J. Immunol. 30,* 345 (1936). The amount of precipitate obtained when a solution of pneumococcus vaccine, types I and III, is mixed with antiserum may be accepted as an approximate accurate indication of the immunizing power of that solution upon oral administration.

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Pneumonia Due to Klebs-Loeffler Bacilli. F. G. Smith, *Ohio State M. J. 33,* 534 (1937). Diphtheria bacilli were found in the sputum from a patient showing clinical lobar pneumonia, who recovered by treatment with diphtheria antitoxin.

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Primary Friedlander Pneumonia. Report of Thirty-two Cases. S. Solomon, *J. Am. Med. Assoc. 108,* 937 (1937). Thirty-two cases are presented in which the Friedlander bacillus was the primary invader in pneumonia. Complete details are given concerning the distinguishing features, the incidence, and the mortality of Friedlander's pneumonia.

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The Availability of Specific Pneumococcus Antibody After Intravenous, Intramuscular and Subcutaneous Injection, Including a Study of the Cutaneous Reactions to Type Specific Polysaccharides Following Serum Injection. R. C. Tilghman and M. J. Finland, *J. Immunol. 31,* 239 (1936).

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Electrophoresis of Purified Antibody Preparations. A. Tiselius, *J. Exptl. Med. 65,* 645 (1937). Antipneumococcus horse and rabbit type specific serum antibody preparations reveal different electrochemical properties from normal proteins.

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Effect of Pneumococcus Autolysate Antitoxin on Pneumococcus Pneumonia in Guinea Pigs. J. T. Weld and H. Gilder, *J. Exptl. Med. 64,* 953 (1936).

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The Ultracentrifugal Concentration of Pneumococcic Antibodies. R. Wyckoff, *Science 84,* 291 (1936).

Color Changes in Ointments—With Special Reference to Bismuth Salts. J. Hall, *Pharm. J. 85,* 30 (1937). The author investigated the several possible factors involved in the discoloration of ointments containing bismuth salts. The ointments studied were Ointment of Bismuth with Camphor N. F., Compound Resorcinol Ointment, Simple Resorcinol Ointment and Compound Bismuth Subgallate Suppository of the B. P. C. All were found on storage to exhibit a change in color. All four of these preparations contain analogous ingredients, namely, a salt of bismuth an alkaline substance, and a phenolic substance or derivative (with the exception of simple resorcinol ointment). Compound Bismuth and Camphor Ointment N. F. and Compound Bismuth Subgallate Suppository were chosen as the ointments to be used in the study. Concerning Compound Bismuth and Camphor Ointment, the following results are summarized:

1. Initial color change occurs rapidly in bright light.

2. Color change only occurs where phenol or a phenol derivative is present.

3. The presence of air does not appear to influence the changes.

4. Ointments stored in the dark show no changes even after long periods of storage.

5. Ointments made with different samples of bismuth carbonate exhibit variation in color and rapidity of change.

6. Samples made with metallic implements are more prone to color changes than those made using non-metallic implements.

7. Camphor and zinc oxide apparently do not exert any influence in the color changes.

8. The color changes once begun are progressive.

With compound resorcinol ointment the following information is presented:

1. The access of air causes discoloration.

2. Ointment stored in darkness still acquires a change of color.

3. Light accelerates the color change.

4. If stored in air-tight jars there is no color change.

The discoloration of Compound Bismuth Subgallate Suppositories was traced to the action of the soap solution used to lubricate the suppository mold.

The theory advanced explaining the various color changes involves the reaction between the bismuth subcarbonate and the phenol to form a colorless phenate which upon exposure changes in color due to oxidation. L. F. T.

The Loss of Vitamin A in the Urine in Certain Diseases. E. Schneider, *Klin. Wschr. 16,* 441 (1937), through *Pharmaz. Zentrh. 78,* 432 (1937). In contrast to vitamin C, vitamin A is when given to healthy persons in overdose not excreted in the urine. However, in certain illnesses such as cancer, tuberculosis and general infections a vitamin A excretion has been observed. This finding cannot be used as definite clinical evidence in the above diseases since it is not found in all cases. The loss in the urine may be traced to liver damage and a change in the permeability of the kidney epithelium. Where a large loss of vitamin A occurs a hypovitaminosis may result. L. F. T.

Preparation of Extracts and Tinctures. C. J. Blok and H. J. A. ter Wee, *Pharm. Weekbl. 73,* 1335 (1936), through *Quart. J. Pharm. & Pharmacol. 10,* 120 (1936). The usual methods for the preparation of extracts and tinctures are not calculated to give the best possible results. The method of applying pressure to assist the flow of percolating liquid was first suggested by Count de Real in 1816 and this is the basis of the diacolation method of Breddin, in which air pressure is used to force the liquid up through a column of the drug in a long cylinder. Another method is that of evacolation (Kessler) in which the drug is also placed in a long cylindrical tube which is then evacuated, the percolation taking place downwards *in vacuo* and with the acid of atmospheric pressure. The following preparations made by the latter process were compared with those made in the usual way: Tinctures of Myrrh, Ipecac, Opium, Fluidextracts of Kola and Ergot. In general the results both in yield and solid content were to the advantage of the evacolation process. L. F. T.

Glycerite of Starch. G. Ganino, *Boll. Chim. Farm. 74,* 465 (1936), through *Quart. J. Pharm. & Pharmacol. 10,* 121 (1937). The different pharmacopœias give different proportions of starch,

glycerin and water and different directions for heating in making this preparation, but there is always difficulty in reaching the temperature necessary to obtain a satisfactory preparation without getting some discoloration owing to local overheating. The author found that the most satisfactory method was to heat in an autoclave. The autoclave is heated to the boiling point, the fresh mixture of starch, water and glycerin is put in, the autoclave is closed and heated to 120 degrees C. for twenty minutes. The pressure is then allowed to escape, the autoclave opened and the glycerite well mixed. The product is uniform, colorless and keeps well. This same method of preparation can be used when medicaments are required mixed with it. For instance, zinc oxide or ichthyol can be added before autoclaving, and perfumes as well without risk of loss, an excellent preparation being obtained. L. F. T.

A Color Reaction of Ascorbic Acid. S. Dietrich and G. Hundhausen, *Klin. Wschr. 16,* 222 (1937), through *Pharmaz. Zentrh. 78,* 432 (1937). The urine of the sick which contains larger amounts of vitamin C gives with sodium nitroprusside an intensive blue color. Pure vitamin C and urine to which vitamin C has been added also gives this reaction. It is just as specific as other methods, e. g., with Tillmann's reagent or methylene blue. Pyrol and indol bodies react similarly with sodium nitroprusside to give a blue color. The sensitivity of the test is about 15 mg./per cent. The test is applied in the following manner: To the sample add 1 to 2 cc. of a solution of sodium nitroprusside (a hot saturated solution diluted one to three) and then dropwise sodium hydroxide solution. If a red color develops creatinine is indicated. Acetic acid is then added drop by drop and in the presence of vitamin C a blue to bluish-green color occurs. It is necessary in conducting the test that acetone bodies be absent from the urine sample. L. F. T.

The Tannic Acid-Silver Nitrate Treatment of Burns. A. G. Bettman, *J. A. M. A. 108,* 1490 (1937). Although the treatment of extensive burns by the tannic acid-silver nitrate method has been described previously, this article presents a very interesting considera-

tion of its rationale. The treatment appears to change the lesion into one comparable to a surgical wound. It is this induced change by the application of tannic acid and silver nitrate that makes it superior to any other procedure from many points of view:

1. The saving of lives that would be lost through the slower method of tanning.

2. The immediate stopping of the loss of body fluids, thereby preventing the consequent concentration of the blood.

3. The immediate prevention or very definite minimizing of shock.

4. The immediate prevention of the absorption of toxic products.

5. The prevention of infection by the short period of application of moisture and the early drying of the tanned tissues.

6. The saving of the kidneys and other organs from the effects of fluid concentration and the absorption of toxins and infection.

7. The greater comfort of the patient.

8. The fact that the patient is carried safely past the first twenty-four hours, the most critical period following a serious burn.

9. The fact that the patient avoids the second critical period, that of infection and late absorption of toxic products.

10. The simplification of the nursing problem, especially in the first twenty-four hours.

11. The prevention of further breaking down of tissues, resulting from long application of wet dressings.

12. The prevention of chilling, resulting from the long application of cold, wet dressings.

13. The formation of a thin, flexible coagulum.

14. The speedy healing of the burned areas with a shortened period of hospitalization.

15. The prevention or minimizing of heavy contracting scars by early rapid healing in the absence of infection.

16. The lessening of the amount of skin grafting and secondary corrective surgery.

The article presents a very interesting description of the technique, the advantages and case histories in which the treatment was remarkably effective. L. F. T.

Small Animal Euthanasia—Veterinary Surgeons' Recommendations. Pharm. J. 84, 649 (1937). The following is, in brief, some of the recommendations published in a sixty-page booklet by a Committee of the National Veterinary Medical Association (England) on the subject of small animal euthanasia after a careful study over a period of several years.

The captive bolt pistol is strongly recommended preceded if necessary by a narcotic. The construction of this instrument is such that a cylindrical steel bolt provided with a sharpened and hollowed-out anterior end is caused to discharge from the barrel of the pistol by the firing of a blank cartridge. The bolt is so constructed that it cannot entirely leave the barrel of the pistol.

A number of narcotics and other drugs were tested by the committee. In the case of hydrocyanic acid it was found that its use might entail a certain amount of pain evidenced by spasms, howlings and obvious distress, however, it was agreed that under certain circumstances the administration of hydrocyanic acid would be the only method that might be adopted. The administration of strychnine was not studied by the committee due to the general experience of all its members who had repeatedly observed the painful and distressing symptoms of animals suffering from acute strychnine poisoning. Magnesium sulfate when injected, preferably intravenously, is a powerful and rapid narcotic poison. A solution containing 100 gm. of the hydrated salt in 100 cc. of water is recommended; 5 to 20 cc. of this solution should be slowly injected intravenously.

The advisability of prenarcotization was investigated and several narcotics were studied in this direction. As the degree of narcosis reached in the dog after the subcutaneous of one to three grains of morphine sulfate was as a general rule insufficient to bring into complete subjection the undesirable features of hydrocyanic acid poisoning, the method is not recommended. Morphine administered to cats usually produces excitant effects and not narcosis.

When solutions of chloral hydrate were administered by mouth, by intrathoracic or intraperitoneal injection, a marked variation in the action of the drug was observed, pain and anxiety being very noticeable. Of all the non-volatile anesthetics tried, Nembutal gave the most consistent and satisfactory results. For cats and dogs the intraperitoneal, intrathoracic, or intravenous routes of administration are recommended and the dose employed should be not less than

one-half grain per pound body weight. The intrathoracic injection of an appropriate dose of hydrocyanic acid in a dog or cat anesthetized by Nembutal is followed by a very brief period of increased respiration and by rapid death. The objectionable symptoms seen in cases of hydrocyanic poisoning alone are invariably absent. Avertin, when intravenously injected in doses of 1 cc. per 15 pounds body weight, produces narcosis in ten to fifteen seconds followed by death. It does not produce good results with cats.

The committee does not consider the inhalation anesthetics as satisfactory as the non-volatile agents since the method is slow even when properly conducted. L. F. T.

On the Colorimetric Determination of Cobalt in Metallic Nickel. J. J. Lurie and M. J. Troitzkaya, *Mikrochemie, 22,* 101 (1937). When sodium pyrophosphate is added to solution of nickel or cobalt salts colored solutions are produced: yellow-green in the case of a nickel salt, and blue-violet in the case of a cobalt salt. If to each of these solutions an equal volume of acetone is added, a yellow-green (nickel) and blue violet (cobalt) precipitate is formed. If the violet precipitate of the cobalt compound is filtered off, no cobalt is found in the filtrate: pyrophosphate produces a complete precipitation of cobalt. But if to the solution with the precipitate, without filtering it, ammonium thiocyanate is added, a part of the cobalt passes from the precipitate to the water-acetone solution in the form of $(NH_4)_2C(CNS)_4$. It is necessary that the amount of thiocyanate should be about five times as great as that of pyrophosphate. The following procedure is suggested by the authors for the analysis of cobalt in metallic nickel. The sample of metallic nickel (4 gm. Ni of the highest grade; 1-1.5 gm. of Ni of the lower grade) is placed in a beaker and treated with 20 cc. (for a 4 gm. sample) or 10 cc. (for 1-1.5 gm. sample) of dilute nitric acid (3:2). When the dissolution is complete, 10 cc. of conc. hydrochloric acid are added, and the solution is evaporated to dryness. The evaporation to dryness is repeated twice more, each time 5 cc. HCl (sp. gr. 1.19) being added, the dry residue is moistened with 3-5 cc. HCl, gently heated, 50 cc. of hot water are added, and the heating is continued to a complete solution of chlorides. After cooling, the solution is diluted to one liter. Measured aliquot parts of the solution are evaporated each to a 10 cc. volume. Some crystals of NH_4CNS and some sodium sulfite

are then added and heated at 80-90 degrees till the color of the solution becomes pure green (Ni ions). Upon cooling 1 gm. of sodium pyrophosphate is put in each flask. The solution is made pink to phenolphthalein with 12 per cent. ammonia. 5 gm. of NH_4CNS are added, the contents of each flask are diluted to 15 cc., well shaken, 15 cc. of pure acetone and 1-2 drops of ammonia are added to each. Then the mixture is vigorously shaken for 1-2 minutes. The upper layer of each tube is transferred to a graduated Eggerz test tube. For comparison, the following procedure is adopted: in a separate flask 3 gm. of ammonium thiocyanate are dissolved in 12-13 cc. of water, 15 cc. of acetone, drop of ammonia solution are added; the solution is transferred to an Eggerz test tube, and a standard cobalt chloride solution is added in small portions from a microburette till the color of the solution in the test tube matches the color of the solutions tested. Two tables are given showing the direct colorimetric determination of cobalt compared with the results obtained by a colorimetric analysis of cobalt after its preliminary separation with α nitroso-β-napthol.

Calcium Ortho-Iodoxybenzoate in the Treatment of Arthritis. Cohen (*Clin. Med. & Surg., 44,* 341, Aug., 1937) reports on a series of 125 cases of classic atrophic arthritis where calcium ortho-iodoxybenzoate was the only drug therapy used. With those patients receiving therapy over a considerable period, 5 per cent. were regarded as cured; 43 per cent. very much improved; and 22 per cent. somewhat improved. This represents a total of 70 per cent. who received definite benefit from the drug. The dose employed was usually from 2 to 4 times that heretofore recommended and varied between 3 and 6 gms. daily. While this increase resulted in a greater incidence of intolerance, it is advocated on the basis of greater therapeutic efficiency. Neither age nor sex appeared to be of significance as regards the efficacy of calcium ortho-iodoxybenzoate and no particular type of atrophic arthritis was benefited more than another. Complete hematological examinations and laboratory tests indicated that the drug has no effect on the red or white blood cells, heart or kidneys even when taken over long periods of time. It is concluded, therefore, that calcium ortho-iodoxybenzoate may be safely used in large doses and is a valuable adjunct in the treatment of atrophic arthritis.

SOLID EXTRACTS

By Ivor Griffith, Ph. M., Sc. D.

Despite the form in which this information is presented it may be accepted as trustworthy and up-to-date. Original sources are not listed but they may be obtained upon request.

On the fly-leaf of a certain Benham's Book of Quotations may be seen the following pharmaceutical effusion—

Apothecary Benham
Has scoured the Universe
For barks and yarbs and simples
In paragraphs and verse
Ten million tons of matter,
In one alembic stuffed
And all the heat of ages
Upon its surface puffed.
And when the smoke has cleared
And chill is on the grate
Apothecary Benham
Collects the distillate
It now makes up this volume
Of tincture, true and terse
A world of wit and wisdom
Dissolved in tiny verse.

All who love "the brotherhood of venerable trees," and who like to be reminded of America unspoiled, should read "Audubon," by Constance O'Rourke. There is real inspiration in this story of a headstrong genius of the great open spaces.

Especially interesting is the account of his visit to "Christopher North," (John Wilson), and there is a subtle suggestion here of a certain method in the making of books.

Constance O'Rourke in her bibliographic researches must have read the Ettrick Shepherd where North, in good humor, wrote:

"There's really no end in natur to the eating of oisters." And she forthwith pictured this pleasant pair filling their gullets with "oisters" and washing them down with "the mildest, the meekest, the

very Moses of ales." Which, of course, is but preserving the dramatic unities.

If the man of the house mutters into his beard because the tobacco in his jar, can or pocket pouch dries out so fast, try dipping the humidifier of the container in a mixture of equal parts of glycerin and water, and the tobacco will stay moist much longer. The idea comes straight from the tobacco industry where glycerin is practically indispensable in the manufacture of smoking tobacco, cigars and cigarettes because of its unique property of absorbing and retaining moisture.

The glycerin-and-water treatment works equally well with any of the usual types of humidifier—blotting paper, felt, sponge, or composition material.

Cigarette smokers report further that a glycerin-dipped humidifier is especially helpful with "the makings," because the tobacco used for rolling cigarettes is very finely ground and hence dries out more quickly.

The newest thing in the treatment of malaria is adrenalin, powerful hormone of the adrenal glands. Instead of giving quinine, standby remedy for malaria, or any of the new quinine derivatives, Professor Ascoli, physician-in-chief of the University Medical Clinic in Palermo, Italy, injects adrenalin daily into the veins of malaria patients, he has reported to the Munchener Medizinische Wochenschrift, German medical journal.

The beneficial effect of adrenalin in malaria, Professor Ascoli believes, is due to the fact that it reduces the amount of blood in the spleen. The spleen is the breeding ground in the body for the malaria parasite or germ, and reduction of the amount of blood in the spleen makes conditions unfavorable for malaria parasites to live and multiply.

Professor Ascoli reports he has found adrenalin useful in chronic as well as newly-acquired cases of malaria and in enlargement of the spleen, anemia and general ill-health following malaria.

The modern alchemy of transmuting the elements from one to another by atomic bombardment is destined to solve one of the riddles of science—why the even numbered elements found on the earth are

greatly more abundant than are the odd-numbered ones. More than 75 per cent. of the earth's shell is composed of oxygen and silicon, whose atomic numbers are even; 16 and 14 respectively. Aluminum, totalling 7.85 per cent., comes next and is odd-numbered, 13. But then come iron and calcium, with even numbers, 26 and 20 respectively.

Thus over 90 per cent. of the earth's crust consists of five elements alone; four of which are even in atomic number.

Sodium perborate, that oxygen-rich mouth cleanser, has been dentist criticized because its constant use is said to be destructive to gum tissues, due to its caustic character. Now we are told of a practical neutralized sodium perborate for everyday oral use.

Mono-calcium phosphate is reported as the agent used to reduce the excessive alkalinity of sodium perborate, regarded as the cause of this compound's caustic action, to a pH approximating that of human saliva. In addition to its value in de-alkalizing the perborate, it was found that the reaction forms insoluble phosphates of calcium, which act as mechanical cleansing agents.

At the same time the insoluble phosphates are being formed by chemical reaction, there is a noticeable increase in the solubility of the sodium perborate, resulting in the production of more dissolved available oxygen than is customarily realized from use of ordinary sodium perborate. Thus, by varying the dilution of the compound, it is possible to regulate the oxygen concentration to suit peculiarities of individual requirements.

The combined factors of increased solubility of the sodium perborate and the formation of insoluble phosphates render the material suitable for use either as a mouth rinse or on the toothbrush as a dentifrice.

Tests have been conducted to determine comparative effects of the mixture and the usual sodium perborate. Application of both to the gums of human subjects showed that, under similar conditions, definite caustic effects resulted in the instance of ordinary sodium perborate, while no harmful effects were caused by the newly discovered preparation.

The use of camouflage in the present Oriental crisis is said to be more effectively exercised by the wily children of Cathay than ever it has been done before. Fire throwers are also in constant use. And the relative newness of these martial weapons is commented upon by correspondents.

But camouflage and fire-spreading are both old arts of war. Listen—At the siege of Jerusalem by Titus, about 70 A. D., a stone-throwing apparatus of considerable power was employed by the Romans, a stone weighing about a hundred pounds being thrown four hundred yards. The low trajectory and velocity enabled the watchers to see it and they would call out, "Here comes the stone," and the defenders would rush to cover. The Romans painted the stone a dull color to make it less conspicuous, and thus may be said to have inaugurated *camouflage*. Greek fire, that is, the combustible materials described in the ancient book of Marcus called "The Book of Fires to Burn Enemies," were used somewhere around the fifth century. Ancient battles differed from the present din of war in that they were practically noiseless, except for the shouting of the combatants.

What Does a Field Weigh? According to the U. S. Department of Agriculture the soil from a one acre field to a depth of a foot weighs approximately four million pounds. Whether this be on a dry or a rainy day is left to the imagination. But more surprising than the above is the statement that the addition of 1000 pounds of 5-8-7 fertilizer to an acre of normal soil adds to the soil essence less than one per cent. each of nitrogen and phosphoric acid and less than one-tenth of one per cent. of potash.

Yet even such insignificant lifts in the chemical content do increase the productiveness of soils.